REMARKS

Claims 4, 6-8, 10-17 and 19-21 are pending after amendment. Claims 19-21 are added. Claims 4, 6-8 and 10-16 are involuntarily withdrawn from consideration.

Claim 17 has been amended by the addition of "G protein-coupled protein p2y9" to more particularly point out and distinctly claim the invention. This clarification does not change the meaning not is new matter but makes the claim easier to understand.

Involuntarily withdrawn claims

The US PTO withdrew applicant's claims 4 and 6-16 from consideration without explanation. Applicant points out that the office action of November 14, 2007 (page 3) asserts that "claims 4, 5, and 7-18 are drawn to a method of using the G protein-coupled protein p2y9 and a mutant thereof." The November 14, 2007 office action states that these method of use claims are pending. The November 2007 office action (page 5) also rejects claims 4-9 on 35 U.S.C. §112, second paragraph grounds "since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass." The office action (page 5) further rejects these claims on 101 grounds as not "setting forth any steps involved in the process...."

In other words, the office action tacitly deems the claims examinable as method claims but asserts that insufficient steps are recited.

In response to the rejections, applicant has provided the steps. Applicant has particularly pointed out and distinctly claimed embodiments within the broader scope of claim 4 by amending the language of "using the G protein-coupled protein p2y9" to recite a more specific type of use in "enhancing the effect of" using the protein by expressing in a cell with specific steps of use.

In response to applicant's addition of method steps to particularly point out and distinctly claim embodiments within the scope of Applicants intellectual property rights, the Examiner has unilaterally withdrawn these same claims, without comment or explanation.

The office action deems claims 17 and 18 an examinable group. In response to this restriction, applicant has added the special technical feature of this examinable group (inhibitors of p2y9 dependent LPA activity) to all independent claims (4, 10 and 16) to allow their rejoinder. All claims now recite the "special technical features" of:

a. carried out by monitoring binding (i.e. detecting the result of binding or measuring binding directly) of test samples to G protein-coupled protein p2y9 having a sequence identity of more than 95 % to the amino acid sequence of SEQ ID NO:1; and

b. the inclusion of inhibitors of p2y9 dependent LPA activity.

The two special technical features of **a** and **b**, which are in amended independent claims 4, 10, 16 and 17, define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The inventions as claimed thus are linked as to form a single general inventive concept as prescribed under PCT Rules 13.1 and 13.2. Thus reconsideration and rejoinder of the withdrawn claims 4 and 6-16 are respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 17 and 18 have been rejected on alleged written description grounds under 35 U.S.C. §112, first paragraph, on pages 2-4 of the office action, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is respectfully traversed.

The office action asserts (page 3, bottom) that "a description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs..." However, applicant's claims recite a type of protein "G protein-coupled protein p2y9, not a DNA. The claims recite an art recognized protein, not a genus of cDNA.

A large variety of alternative sequences of the recited protein species is presented within the specification as filed. Applicant has incorporated 24 well known, reviewed and accepted scientific papers that teach a variety of protein species within this genus. Applicant has found that the members within this art defined genus (less than 5% sequence structural primary sequence

variability) respond by binding to lysophospholipid. The claimed invention is not to a new type of discovered protein but to discovered biochemical functioning of a known type of protein with a known variety of protein sequences within the stated 95% homology range. Applicant does not argue numbers of cDNA sequences. Applicant has not discovered a new type of protein and is not defining for the first time, a new type of protein. Applicant has not discovered and does not attempt to define a new genus or species of cDNA. The art already has recognized a type of protein with a variety of alleles within 95% homology. These data are incorporated within the specification. Applicant is merely following the art recognized definition of this protein and has incorporated by reference the multiple species (that make up the recited protein) referred to by the office action. Applicant stands behind the 24 references that are incorporated by reference and does not depart from known science.

As to "G protein-coupled protein p2y9" of this invention, reference is made at least to U.S. Patent Application Publication No. 2006/0264361, the publication for the present application, at paragraphs [0006] and [0011] as follows:

> [0006] It has been recognized that LPA exhibits its physiological activities by binding to G-protein-coupled receptor (GPCR) expressed on the surface of the cell membrane. Namely, the receptor of LPA has been recognized as a seven transmembrane GPCR, however, remained substantially unknown over a long period of time. It is because, LPA being a kind of lysophospholipids and fat-soluble, even the existence of its receptor has been doubted due to the difficulties in carrying out membrane binding assay or in finding a suitable antagonist.
>
> [0011] p2y9, a GPCR of the present invention, is located in the lower left in FIG. 1. Thus, it is apparent from FIG. 1 that p2y9 shares no homology in amino acids sequences with known EDG family or PSP24.

According to these paragraphs, it is clear the words of "G protein-coupled protein" are used as synonymous words of "G-protein-coupled receptor (GPCR)" and "a seven transmembrane GPCR" which is well-known by those skilled in the art of this invention at the time of the invention. Thus the words of "the p2y9 protein comprises an amino acid sequence having a sequence identity of more than 95 % to the amino acid sequence of SEQ ID NO: 1" in claim 17 provide meanings that the amino acid sequence includes the characteristics that there are seven transmembrane regions regularly, each of which comprises amino acid sequence rich in hydrophobic amino acid.

In other words, G protein-coupled protein p2y9 is a well-known protein with an as of yet unknown ligand. It is a seven transmembrane receptor that engages in signal transduction within the cell. G protein-coupled protein p2y9 is well known to people of skill in the art; in fact, a number of alleles of p2y9 of known amino acid sequences, all sharing the same structure and the same function were known before the filing of the present application. A typical human p2y9 allele, which has the amino sequence of SEQ ID NO: 1 is a membrane receptor. This protein shares very little amino acid sequence homology with other G protein-coupled proteins of the same family but has very high homology with p2y9 G protein-coupled protein alleles from other species, as suited for the common structure and common function that evince their common identity. Applicant provides the Examiner with a number of amino acid sequences of p2y9 from a variety of alleles were known before the filing of the present application as Schedule A of this response. As seen in those alignments a skilled artisan would readily determine whether an amino acid sequence of a known protein is a G protein coupled protein p2y9 protein. Since these proteins do have minor modifications between alleles, the protein can be specified in claims only by the name of the protein and not by a specific amino acid sequence. Defining the protein in terms of one allelic amino acid sequence therefore would violate the known science of this protein as well as unduly limit the scope of the claim.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 17 and 18 are rejected under 35 U.S.C. §112, second paragraph as being indefinite because they recite "substances." The rejection is respectfully traversed.

The word "substances" has been amended to "a candidate compound" as suggested by the Examiner.

Claim 17 was rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 18 was likewise rejected. The rejections are respectfully traversed.

Claim 17

Claim 17 has been amended to include steps (a) through (g) by the foregoing amendment. No new matter has been introduced. Support to the steps can be found in U.S. Patent Application Publication No. 2006/0264361, the publication for the present application, at paragraphs [0117] and [0119] through [0129]. Namely, step (a) of claim 17 is supported by Example 1 (paragraphs [0119] and [0120], steps (b) through (d) of claim 17 are supported by Examples 2 through 4 (paragraphs [0121] through [0129], and steps (e) through (g) of claim 17 are supported by paragraph [0117]. Likewise supports to newly added claims 19-21 can be found in these paragraphs. No new matter has been introduced. Thus Applicants submit that claim 17 is allowable.

As stated above, in connection with the paragraphs [0006] and [0011], it is clear that the words of "G protein-coupled protein" are used as synonymous words of "G-protein-coupled receptor (GPCR)" and "a seven transmembrane GPCR" which is well-known by those skilled in the art of this invention at the time of the invention. Thus the words of "the p2y9 protein comprises an amino acid sequence having a sequence identity of more than 95 % to the amino acid sequence of SEQ ID NO:1" in claim 17 provide meanings that the amino acid sequence includes the characteristics that there are seven transmembrane regions regularly, each of which comprises amino acid sequence rich in hydrophobic amino acid.

The methods for measuring physiological activities, such as, intracellular calcium mobilization or intracellular cyclic AMP (cAMP) concentration, are well known methods to measure degree of bonding between the cell surface receptors and ligands. Examples of the measurements, such as, changes in intracellular calcium mobilization or intracellular cyclic AMP (cAMP) concentration are described in the Specification, in connection with Examples 2-4 in the specification (paragraphs [0121] through [0127] which are reproduced below). In the Examples 2-4,

"p2y9" has been recognized as a "LPA receptor" according to well-known measurement methods. In other words, according to well-known methods, bonding between "p2y9 as a receptor of LPA" and "LPA" has been measured in connection with intercellular calcium concentration or intercellular cyclic AMP (cAMP). U.S. Patent Application Publication No. 2006/0264361, the publication for the present application, at paragraphs [0121] through [0127] read as follows:

Example 2

* * *

[0121] CHO clones of four individual receptors such as GPR34, p2y5, p2y9 and p2y10 were seeded respectively in three 96-well plates at a density of 4.times.10.sup.4 cells/well. On the following day, cells were loaded with 4 μM of Fluo-3 (calcium indicator) and incubated at 37.degree. C. for 1 hour for incorporation of Fluo-3. Cells were then reacted with individual lipids (1 to 10 μM) contained in the Lipid Library of BIOMOL comprising over 200 kinds of lipid molecules and 17 nucleotides (1 to 100 μM) such as ATP, then **time course kinetics of intracellular calcium mobilization was monitored** with FLEXstation of Molecular Devices.

[0122] CHO cells endogenously expressing ATP receptors, the remarkable change in intracellular calcium concentration beyond the measurable range has been detected in ATP added clones. This enabled to confirm the relevance of the experiment.

[0123] On the other hand, unlikely to the case of ATP, the intracellular calcium increase, not in entire clones but, specific to the expressed receptors was recognized when p2y9-expressing clones was reacted with LPA.

Example 3

[0124] Determination of LPA-Dependent Calcium Concentration Changes in Individual Clones

[0125] CHO clones stably expressing four types of receptors such as GPR34, p2y5, p2y9 and p2y10 respectively were used to monitor **the intracellular calcium concentration change** in each cell in the same manner as described in Example 2.

[0126] The result was shown in FIG. 3.

Example 4

Determination of the Changes in cAMP Concentration in Each Clone

[0127] CHO clones stably expressing four types of receptors such as GPR34, p2y5, p2y9 and p2y10 respectively were suspended in HBSS containing 5 mM HEPES-NaOH (pH 7.4), 0.1% BSA and 500 μM IBMX (inhibitor of cAMP degradation enzyme). The cells at the density of 1.times.10.sup.5 cells/well were seeded in 384-well plates, and reacted with 59 lipids selected from the Lipid Library of BIOMOL or 17 nucleotides under coexistence of 50 μM forskolin (receptor-independent adenylate cyclase activator) at room

temperature for 30 minutes. **The intracellular cyclic AMP (cAMP) concentration was then measured** using an AlphaScreen cAMP assay kit (Packard).

(Emphasis added.)

Thus the processes of (a) through (g) according to claim 17 as amended are supported by the specification in connection with the Examples 2-4 and the amendment to claim 17 does not constitute new matter. Further the amendment to claim 17 clarifies the process as claimed prior to the amendment, it does not raise any new issue to require additional search or examination.

Canceled Claim 18 and Reintroduced Claim 21

Claim 18 has been canceled and replaced with new claim 21.Claim 21 is dependent from claim 17. Thus Applicants submit that claim 21 is likewise allowable.

The ambiguity of claim 18 has been clarified in claim 21. Thus no new mater has been entered and no new issue that requires new search or examination. The words "further screened for effects on carcinoma cell invasion" in claim 18 now canceled were not intended to add new screening process to claim 17 but to further define "inhibitors of p2y9 dependent LPA activity" of claim 17 to be "inhibitors of carcinoma cell invasion." In other words, as a result of screening "inhibitors of p2y9 dependent LPA activity," "inhibitors of carcinoma cell invasion" are screened, as claimed in claim 18. Responsive to rejection of claim 18 and to clarify the subject matter of claim 18 now canceled, claim 21 has been added. In claim 21, the ambiguity of claim 18 has been removed. Thus neither new matter nor new issue requiring further search or examination has been added.

Newly Added Claims 19 and 20

Newly added claims 19 and 20 are dependent from claim 17 and further define the Examples 2-4 which are discussed above. No new matter has been added. Thus Applicants submit that claims 19 and 20 are likewise allowable.

Rejection under 35 U.S.C. §102 (b)

Claim 17 is rejected on alleged anticipation grounds in view of a reference that described binding to a p2y9 protein.

Amended claim 17 further includes steps of (a) through (g). Because all claims recite steps that are lacking (and even taught from) in the cited references, reconsideration and allowance are requested.

Dependent Claims 19-21

Since new claims 19-21 depend on claim 17, they are allowable for at least the reasons that claim 17 is allowable respectively and it is further allowable by reason of the additional limitations set forth therein. Therefore, withdrawal of the rejection of claim 17 and allowance of the claims is respectfully requested.

Claim Language Changes: "LPA dependent LPA activity" to "p2y9 dependent LPA activity"

The change of the words of "LPA dependent LPA activity" to "p2y9 dependent LPA activity" in claim 17 by the foregoing amendment was made to correct obvious error does not raise new issues to require new search and examination, because the error is quite obvious for one skilled in the art to recognize as and error.

The change is not new matter inclusion. Support for the change also supported by the specification. Reference is made at least to U.S. Patent Application Publication No. 2006/0264361 at paragraph [0117], which reads as follows:

> [0117] p2y9 being a receptor of LPA, p2y9 of the present invention can be used to screen various physiological activities stimulated or inhibited by LPA. The method of screening of the present invention can be performed by letting p2y9s expressed in the cell, or using the cell or membrane already having p2y9s therein. The screening method of the present invention are not limited to any particular ones as described above, but include the methods to screen the substances having activities with LPA **by using p2y9 as a receptor of LPA**. (Emphasis added.)

The words of "by using p2y9 as a receptor of LPA" above are used to mean that, by LPA being bonded to p2y9 sitting in a membrane already exists as a receptor of LPA, various physiological activities, which occur instantly, such as, changes in intracellular calcium mobilization or intracellular cyclic AMP (cAMP) concentration as described in connection with Examples 2-4 in the specification (paragraphs [0121] through [0127]). In other words, the measurements of these activities "by using p2y9 as a receptor of LPA" can be easily performed by measuring changes in, such as, intracellular calcium mobilization or intracellular cyclic AMP (cAMP) concentration, which are well known methods to measure degree of bonding between the cell surface receptors and ligands.

The words of "LPA dependent LPA activity" which were used prior to the foregoing amendment were used since the measurable intercellular physiological activities occur by "LPA" being bound to cell surface "p2y9." However, it is unclear what to mean by the words of "LPA dependent LPA activity" on the face, the words are now substituted with the words "p2y9 dependent LPA activity" to stress that the measurable intercellular physiological activities occur by "LPA" as a ligand being bound to cell surface "p2y9" as a receptor of "LPA." Thus the amendments were intended to clarify the ambiguous terms requiring new search or examination.

Summary and Conclusion

Entry and favorable review of these amended claims earnestly are requested.

All other claims have been amended to include the elements of amended claim 17. All claims thus include common special technical features that define a contribution, which each of the claimed inventions, considered as a whole, makes over the prior art. Accordingly, the claims are linked as a single inventive concept as prescribed under PCT Rules 13.1 and 13.2. Reconsideration and rejoinder of the withdrawn claims 4 and 6-16 are respectfully requested.

The Examiner cordially is invited to contact the undersigned if another telephonic conference can advance this case.

Dated: August 15, 2008

Respectfully submitted,

By _____
Maulin M. Patel
Registration No.: 56,029
RADER, FISHMAN & GRAUER PLLC
Correspondence Customer Number: 23353
Attorney for Applicant